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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/705,519 | 11/10/2003 | James M. Robl | 50195/023003 | 4828 |

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| EXAMINER | |
|---|---|
| CROUCH, DEBORAH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/705,519 | ROBL ET AL. | |
| | Examiner | Art Unit | |
| | Deborah Crouch, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *7-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 25-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *November 10, 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group I, claim 6, in the reply filed on April 27, 2006 is acknowledged. Claims 1-5 and 25-38 are linking claims. Claims 7-24 have been withdrawn from consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 25-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are to a bovine comprising a non-naturally occurring mutation at one or both alleles of an endogenous prion nucleic acid, where the mutation is an insertion of a positive selection marker into a prion nucleic acid, bovine cells, methods of producing the transgenic bovine having reduced expression function prion protein.

The specification teaches the production of the claimed bovines by nuclear transfer using bovine fetal fibroblasts comprising an insertion into the endogenous prion allele. However, the methodology disclosed, knockout coupled with nuclear transfer, was shown by the art to be unpredictable at the time of filing. Clark teaches that only primary somatic cells have been used successfully in gene targeting experiments to produce livestock having a disrupted gene of choice (Clark, page 265, col.2, parag. 1, lines 12-15.) In addition, Clark teaches that about 45-population doubling are required to generate targeted cells (Clark, page 268, col. 2, parag. 1, lines 1-5). Denning teaches primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence (Denning, page 222, col. 1, lines 5-8). In a study of sheep

and goat primary somatic cells, Denning found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. Sheep primary cell cultures primarily were composed of fibroblasts after the third passage or about 12 doublings (Denning, page 224, col. 2, lines 11-13). Further, a comparison of separate Black Welsh sheep primary cell fibroblast cultures showed vast differences in the number of doublings prior to senescence; 110 doublings versus 40 doublings (Denning, page 224, col. 2, lines 16-19). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (Denning, page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). The studies were performed with constructs designed to disrupt the prion gene or the 1,3 α-galactosidase gene (Denning, page 226, figure 4 and page 227, col. 2, parag. 1, lines 1-3). Additional studies of cell cultures prepare from fetal pig organs (gut, kidney, lung and mesonephros showed that these cells senesced or entered crisis after even fewer doublings than the fibroblast cultures (page 225, col. 1-2, bridg. sent.). Further, even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for nuclear transfer, meaning that targeting frequency was lower than expected (Denning, page 228, col. 1-2, bridg. sent.). Similar experiments in pigs demonstrated all the clones senesced, and no targeted cells for nuclear transfer were obtained. In experiments for the production sheep comprising a disruption of the α1,3-galactosyltransferase gene, live births were achieved but the animals died within two weeks of birth (Denning, page 230, col. 1, parag. 2, lines 1-8). However, Denning reports that McCreath achieved live birth and survival of two gene targeted sheep with disruptions in different genes (Denning, page 230, col. 1, parag. 2, lines 9-12). Denning analyzed the

results of both sheep experiments and arrives at the conclusion that it is possible that for gene targeted sheep, the success depends on unknown factors, whereas in pigs, the use of fibroblasts to produce gene-targeted pigs is not possible (Denning, page 230, col.1, parag. 1, lines 7-13). Denning continues to state that for sheep the parameters of cell growth and targeting efficiency reported therein just about make feasible the production of gene targeted sheep. For pigs, Denning continues to state that the lower proliferative capacity indicates that gene targeted pigs are only marginally likely. There is evidence of one bovine fetus comprising a disrupted $\alpha$-1,3 galactosyltransferase gene being produced by disruption of the gene in bovine fetal fibroblasts, and the fibroblast being used in a nuclear transfer method to produce the bovine fetus. However, the method lacks evidence of reproducibility as multiple embryos were transferred but only one fetus produced. Further, production of the fetus does not mean that a live-born or a useful live-born bovine would be produced given the lack of such success as reported by Denning and McCreath. While a cow is not a sheep or a goat, the species is not seen as the important factor here. The issue with gene targeting, regardless of cell type or species, is that only embryonic stem cells and fibroblasts are known to have sufficient population doubling for selection (see Clark, above). The teachings of Denning demonstrate that in two species, even fibroblasts undergo senescence prior to selection of cells comprising the targeted disruption. Although one of The lack of predictability in producing a useful live born bovine is noteworthy in view of the specification's disclosure that cows lacking functional prion protein are to be used as bioreactors, and agricultural products (page 1, lines 15-19). A cow that does not survive birth or survives only a few days after birth would not have a use in the art.

In addition, Dunne (US 2002/0194635) states that mice lacking functional prion protein appear normal; there is evidence of an altered sleep-wake cycle and circadian rhythms (page 3, parag. 0031, lines 8-11). Dunne goes on to state that such an alteration

in cows would have serious consequences (page 3, parag. 0031, lines 11-12). Dunne also states that one form of human TSE shows large changes in sleep and daily rhythms of several hormones (page 3, parag. 0031, lines 11-12). Thus, the knockout of the endogenous prion gene in bovines could result in another form of BSE.

Further, applicant's method is only enabled for enucleated MII oocytes. The stage of oocyte development is important to nuclear transfer, as exposure to the ooplasm of MII oocytes reprograms the donor nucleus. In particular, the use of nucleated oocytes would result in polyploidy embryos that would not support term development.

Thus, at the time of the instant invention, the skilled artisan would have been required to engage in an undue amount of experimentation without a predictable degree of success to implement the invention claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 25-32 and 35-38 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by US 2002/0069423 (Good).

Good teaches heterozygous and homozygous bovines comprising an insertion of a positive selection marker into one or both alleles of an endogenous prion gene, where the bovines lack functional prion protein (page 6, parag. 0052, lines 1-4, page 18, parag. 00196 and page 19, parag. 0208).

Good also teaches a bovine fetal fibroblast comprising an insertion of a positive selection marker into one or both alleles of an endogenous prion protein gene, where function prion protein is not expressed (page 7, parag. 0074, lines 1-3; page 8, parag. 0091; page 9, parag. 0097, lines 16-20; and page 16, parag. 0165-0169).

Good teaches a method for producing a transgenic bovine cell having reduced expression of function prion protein comprising introducing into a first prion gene the insertion of positive selection marker targeting vector into a bovine fetal fibroblast under conditions that allow homologous recombination to produce a fibroblast having a hemizygous mutation and a homozygous mutation (page 16, parag. 0164-0167).

Good teaches the production of a transgenic bovine having reduced expression of functional prion protein comprising inserting a fetal fibroblast cell or it nucleus into an enucleated oocyte, wherein said cell comprises an insertion of a positive selection marker into a prion protein allele, transferring the oocyte to a surrogate mother and permitting term development (page 18, parag. 0184-0196).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 7:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

June 7, 2006